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Annual Report
of the
COMMISSION ON NEUROTROPIC VIRUS DISEASES
of the
Board for the Investigation and Control of
Influenza and Other Epidemic Diseases in the Army
in the Preventive Medicine Service of the Office of the Surgeon General
covering the period of May 1st, 1943, to April 1st, 1944
prepared by
John R. Paul, M.D.
Director

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U. S. Army

April 14, 1944

PERSONNEL

During the past year the Commission has sustained another serious loss in the death of Dr. Leslie T. Webster, who was an associate member of the Commission.

Capt. W. P. Havens, Jr., M.C., has become an adjunct member of the Commission having been detached from the 38th General Hospital, U.S.A.F.I.M.E., and assigned to the Infectious Hepatitis Laboratory of the Commission at the Yale University School of Medicine.

Major M. Sanders, M.C., has been temporarily detached from the Commission and is now assigned on another project at Camp Detrick, Frederick, Maryland.

ACKNOWLEDGMENT

The National Foundation for Infantile Paralysis contributed the sum of \$15,000.00 to aid in the work of the Middle East Expedition of the Neurotropic Virus Disease Commission. Grateful acknowledgment is made of this grant.

REPORT OF ACTIVITIES

Expedition to the Middle East and Mediterranean Area.- In February, 1943, two members of this Commission were directed to proceed to Egypt and North Africa. These members included Dr. J. R. Paul (Director), and Major A. B. Sabin, M.C., who together with Major C. B. Philip, Sn. C. (entomologist), made up a group of three.

The Commission left the United States on April 22, 1943, arrived in Cairo, Egypt on April 28, 1943, and reported for duty to Col. Crawford F. Sams, M.C., Chief Surgeon of the U.S.A.F.I.M.E. Under his direction, and later under the direction of Col. D. W. Billick, M.C., the Commission established and maintained its laboratory and experimental ward in connection with the 38th General Hospital at Camp Russell B. Huckstep, the desert camp in the vicinity of Cairo. This building was ready for use on May 20th and was maintained as an active laboratory until December 15th.

During the course of their investigations and surveys, members of the Commission visited, besides Egypt, Palestine, Iraq, Iran and India to the east; the Anglo-Egyptian Sudan and Eritrea to the south; Libya, Tripoli, Tunisia, Algeria and Sicily to the west.

Major A. B. Sabin returned to the United States on September 29th, in order to carry on part of the work in the United States. Major Philip was transferred to the Typhus Commission with headquarters in Cairo, on December 15th, and Dr. Paul, accompanied by Capt. W. P. Havens, Jr., M.C. (on detached service with the "Virus Commission") returned to the United States on February 14th, 1944.

Program of Work by the "Virus Commission".- Three diseases were designated to receive special attention. These were:

- A. Sandfly fever.
- B. Poliomyelitis.
- C. Infectious hepatitis.

Two of these diseases, A and B, are definitely virus diseases, the third is presumably a virus disease. All three are epidemic and endemic in the Middle East and Mediterranean area. Sandfly fever and infectious hepatitis have been studied as military diseases, by British, French, Russian and German investigators, but prior to April, 1943, no American Army investigators had had occasion to record observations on any of these infections in this area, or to apply some of the newer virus techniques, familiar to us in this country.

Phlebotomus (Pappataci or Sandfly) Fever. - Field observations on epidemics of sandfly fever among American troops were first made by members of the Commission in Egypt and Persia, and later in Sicily. Experimental transmission of this disease was next carried out in the Middle East laboratory. These experiments revealed that the virus (contained in the serum of patients during the first 24 hours of the disease) readily reproduced the disease in human beings — American Army volunteers.* Sandflies (Phlebotomus papatasi) reared in the Commission's laboratory transmitted the disease from infected to normal human beings, while mosquitoes (Culex pipiens) and (Aedes aegypti) collected in an epidemic area, and fleas (Pulex irritans) obtained from native clothing did not.

Studies on the effectiveness of insect repellents applied to the skin as a means of protecting troops against sandfly bites were carried out. One standard preparation, dimethyl phthalate, was found to be effective over a period of 6 to 8 hours.** Its use in the control of an outbreak of sandfly fever among American troops was investigated by the Commission. The results were encouraging.***

*The participation of American soldiers in this investigation was supported by commanding officers of the U.S.A.F.I.M.E. Most of the volunteers received the Legion of Merit for this work.

**Sabin, A.B., Preliminary Observations on the Effectiveness of Certain Repellents on Phlebotomus papatasi. Submitted to S.G.O., May, 1943.

***Paul, J.R., Philip, C.B., and Sabin, A.B., Dimethyl Phthalate as a Repellent in the Control of Sandfly Fever. Submitted to S.G.O., April, 1944.

Several strains from Sicily and the Middle East were brought to this country and in subsequent work carried on by Major Sabin at Cincinnati sandfly fever has been repeatedly reproduced (as fever therapy) in the treatment of patients with CNS disease. The following new facts have been learned: (1) sandfly fever is easily reproduceable; (2) the virus is found in the blood at least 24 hours before the onset of fever, during the first 24 hours of fever, but no longer than 48 hours after onset; (3) the virus has been passaged in series 7 times by the inoculation of serum from human being to human being without any apparent change in its properties; (4) the dose of the virus (i.e., infected serum) which produced the disease when inoculated intracutaneously or intravenously in 95% of human adults failed to produce the disease in 50 to 75% of individuals in simultaneous tests when the inoculation was given subcutaneously or intramuscularly; (5) the size of the virus as determined by gradocol membrane filtration tests has been determined as being not larger than 40 to 60 m μ , and quite probably not larger than 25 to 37 m μ , thus falling into the same range of magnitude as that of yellow fever which is 22 m μ ; (6) all animal inoculations with this virus have been negative. Some inoculations of the third and fourth passage chick embryo cultures have not reproduced the disease.

Clinical observations on the experimental disease have enhanced our knowledge of the symptomatology. More than 100 cases of the experimental disease have been observed in which the duration and character of the fever have been carefully charted and new information of diagnostic importance has been obtained about the differential and total white blood counts.

From the standpoint of immunity, 19 subjects inoculated the second time with virus (of proved potency) at intervals of from 17 days to 4 months after the first attack were all immune. However, two physicians residing now in U.S.A. who gave a history of two natural attacks of the disease while in the Middle East (four and seven years before respectively) were tested

with the Middle East strain. One of them developed a typical case of average severity while the other had an abortive attack lasting only a few hours. People who recovered from infection with either the Sicilian or Middle East strain of Phlebotomus fever virus were not resistant to inoculation with dengue fever virus. Further studies on natural immunity and artificial immunity in sandfly fever are in progress.

Poliomyelitis in the Middle East.- This disease proved common in Egypt, Libya, and Palestine; frequent cases, many of them fatal, having occurred in British and American troops. The Commission was also concerned with diagnostic problems offered by a number of borderline or atypical cases of poliomyelitis, (encephalitis or neuritis). Here the diagnosis was often difficult and the nature of the disease obscure. The experimental work done on poliomyelitis is recounted later in this report, under the heading of "Poliomyelitis Investigations."

Infectious Hepatitis.- The Commission is impressed by the magnitude of this problem as a military disease in the Middle East and Mediterranean area. Hundreds of military cases were seen in Egypt, and thousands in North Africa and Sicily. Epidemics were investigated in Sicily and a report of the findings has been submitted.*

Comparisons between the experimental and natural disease were made. Data on the length of the incubation period were accumulated and it seems definite that the incubation period is shorter in the natural disease than in the experimental, for in the natural disease it may be less than 40 to 70 days, based on the time at which Air Corps officers and men contracted the disease after arriving in North Africa from the United States. Longer incubation periods (60-100 days) were encountered in the disease experimentally produced in the Commission's laboratory in seven instances.

* Paul, J.R., and Havens, W.P., Preliminary Report on Infectious Hepatitis, submitted to S.G.O., December, 1943.

For the continuance of this work, a laboratory for the study of infectious hepatitis has been established at Yale University, School of Medicine, under the direction of Dr. Paul and Capt. Havens.

Epidemic Encephalitis. - Epidemiology - by W. McD. Hammon: New information with regard to the mosquito transmission has been obtained. Approximately 80 strains of Western Equine and St. Louis encephalitis virus have been isolated from mosquitoes in Washington, California and Nebraska. One W.E. virus each has been isolated from a single species of Theobaldia, Anopheles and Aedes and one W.E. and S.L. from C. pipiens. The importance of C. tarsalis as a host and the relative unimportance of other species in these areas is substantiated. Studies on feeding habits by means of precipitin tests, demonstrated that C. tarsalis feeds predominantly on birds and Aedes rarely on birds. Since antibody studies on domestic birds, together with population estimates show them to represent the largest body of infected vertebrates, and since virus can be most readily isolated from their blood after a minute subcutaneous inoculation (10^{-7}), it becomes obvious why C. tarsalis, with a predilection for birds, is found infected, rather than Aedes, which shuns birds. After amply demonstrating that C. tarsalis can acquire infection from a bird in the laboratory and transmit it to others, its rôle as a vector in nature is satisfactorily established. This applies to both W.E. and S.L. viruses. Culex pipiens, having been found infected with S.L. virus and proved capable of transmitting it can now be considered a natural vector of this virus. The same can be said of Theobaldia inornata for the W.E. virus. The comparative importance of these vectors probably varies depending on local conditions. There are probably other vectors, some possibly quite important.

One new virus has been isolated from a California mosquito. There is no evidence as yet as to whether this is pathogenic for man.

No answer has been obtained to the question of how these viruses are carried over winter. It seems probable that most Culex tarsalis do not

survive the winter as adults in the Yakima Valley area, since only 18 could be found during the winter where 5,000 C. pipiens (a comparatively rare species in the area) were found.

New information with regard to the mosquito transmission of Japanese B virus has also been obtained by Hammon. This new information is very pertinent, for it now appears that if this disease is introduced into this country it might readily be transmitted in nature by some of the same mosquitoes and from some of the same reservoirs which are now utilized by Western Equine and St. Louis viruses. Dr. Hammon believes and this belief has been supported verbally by Dr. A. A. Smorodintsev of Moscow, who has been faced with the control of this disease in Siberia, that serious consideration must be given to the menace of the possible introduction of Japanese B encephalitis into the United States.

In recommendations for the control of arthropod-borne virus encephalitides among military personnel, Hammon has indicated that total mosquito control should be practiced. Anopheles breeding is being adequately suppressed in most areas where troops are stationed in the United States but often Medical and Sanitary officers disregard culecine breeding as harmless, since this has been taught them by schools and texts. This situation should be changed.

In combat areas where mosquito abatement is not possible, the excellent new repellents and insecticide sprays should play an important part. Nevertheless, situations may well arise under such adverse conditions that all these measures would fail. It is problematic according to Hammon that under such adverse circumstances accurate diagnosis would be made and that vaccine of the proper type in the proper condition could be made available and be used in time to alter the immediate situation. If the involved area is still one of active combat where mosquito control is impossible the following season, a trial of vaccination as soon as the first case was recognized would seem to be indicated.

Epidemic Encephalitis Vaccines - W.E.E. Vaccines.- In work carried on by Drs. Olitsky, Morgan, and Schlesinger of the Rockefeller Institute, the immunogenic capacities of chick embryo and allantoic fluid vaccine were compared both in laboratory animals and on their ability to produce neutralizing antibodies in human volunteers. The outcome of these tests showed that the immune response to the two vaccines was of the same order of magnitude with a slight margin in favor of the chick embryo vaccine.

Some new data were also obtained on the patients vaccinated in Canada in 1942. These were bled after one year and their sera was found to have a neutralization index only slightly lower than that recorded many months previously. (See 1942 Report)

In experiments on untoward reactions in the use of these vaccines carried out by Dr. Ward on two comparable groups of Connecticut State Mental Hospital patient and two smaller groups of prisoners in New Jersey, 238 subjects received allantoic fluid and 244 subjects chick embryo vaccines. No significant differences in the incidence or character of the reactions were observed. Allantoic fluid vaccines produced 12 untoward reactions, (5%); chick embryo vaccines, 18 reactions, (7%). These reactions to both were mild and of brief duration.

A field study designed to test the efficiency of W.E.E. chick embryo vaccine during an "epidemic", was carried out in Kern County, California under Dr. Hammon and Dr. Ward. The experiment was started following the occurrence of 5 cases of encephalitis in this county. A total of 250 workers was vaccinated, and 295 formed the control. In the succeeding months, no cases of encephalitis occurred in either group.

It is evident that different strains of W.E.E. virus differ in their immunizing capacity and this question is still being explored by Dr. Olitsky and his co-workers. Vaccines have been made in embryonated eggs from four strains of W.E.E. virus: (1) R.I., (2) Lederle, (3) Kelser, and (4) from a

mosquito, isolated by Hammon, and mice have been vaccinated. None of the vaccinated mice resisted the R.I. strain but the other viruses resisted in varying degrees. No conclusions are warranted about this study as yet.

St. Louis and Japanese B Encephalitis Vaccines. - The development of mouse brain vaccine for S.L. and Japanese B encephalitis has been the subject of study by Major Sabin in his Cincinnati laboratory for a period of a year and a half.* During the spring of 1943 a trial of these vaccines (prepared on a large scale by the Sharp and Dohme Company) was made by Dr. Ward on volunteers in a New Jersey State prison and patients in the Philadelphia State Mental Hospital. The incidence of untoward reactions was 5.4% in 501 individuals inoculated with the S.L. vaccine and 3.3% in 505 subjects inoculated with Japanese B vaccine. All of these reactions were mild with one notable exception in which, as a result of the S.L. vaccine, a post-vaccinal encephalomyelitis developed. This patient has made a slow recovery and is now able to work although some difficulty is still experienced in climbing stairs.

The neutralizing antibody response, as measured after two weeks in 20 individuals receiving each type of vaccine, was almost negligible and quite different from that experienced by Major Sabin in earlier work. This poor response may be related to some factor introduced when vaccines are produced on a large scale. A similar poor response was encountered in animals. Owing to the press of other work further investigation on these vaccines is not being pursued by the Commission at the moment, but it will be pursued when it is possible to do so.

Dr. Casals at the Rockefeller Institute has also been able to obtain supplemental information on the use of mouse brain vaccines through his studies on Russian spring-summer encephalitis virus, a strain which was obtained by the Board, for the Commission in May, 1942. This strain represents the virus used for vaccination in Russia with successful clinical

*Sabin, A.B., et al, J.A.M.A. (June 19) 1943.

results. Casals' studies have largely dealt with attempts to correlate resistance to infection with neutralizing antibodies in vaccinated mice.

Relationships among Encephalitis Viruses.- Studies on the virus of Venezuelan encephalitis and serological relationships among other encephalitic viruses have also been carried out by Dr. Casals. These viruses fall into three main groups: Group 1, Russian spring-summer encephalitis virus and louping-ill virus; Group 2, Japanese B virus, St. Louis virus, and West Nile virus; Group 3, Western Equine virus.

Summary of Epidemic Encephalitis in the Army.- These infections have not been frequently encountered in the Army (in 1942 and 1943) but they will continue to be a potential menace. It will be the function of the Commission to maintain laboratories which will assist in:

1. Aiding in the serological diagnosis of the disease.
2. Studying the epidemiology and recommending methods of control, particularly mosquito control.
3. The development of vaccines.

Lymphocytic Choriomeningitis.- Dr. C. A. Janeway and Mrs. Mary B. Meyer have reported the following significant findings:

1. Although cases of lymphocytic meningitis, variously labelled as lymphocytic choriomeningitis (LCM) or meningoencephalitis, were reported in 1943 at the rate of from 1 to 10 per week in the Army for the whole United States, there is good reason to believe that most of these were not caused by the virus of LCM.

2. Attempts to isolate LCM virus from the cerebrospinal fluid of 18 cases of benign lymphocytic meningitis in the Boston area were negative in all but one.

3. Sera have been studied by complement fixation in 61 cases in which lymphocytes were found in the C.S.F. All but one were negative to LCM. It is important, however, that 10 of these sera showed complement fixing

antibodies for mumps, (Enders), and thus mumps appears to be the chief cause of benign lymphocytic meningitis, in the Army in the United States.

In view of the fact that after investigating the matter for a period of a year and a half it does not appear that lymphocytic choriomeningitis is a disease requiring the special attention of this Commission, the laboratory for the study of this disease will be closed as of July 1st.

Epidemic Keratoconjunctivitis.- by Major M. Sanders: This laboratory has done valuable work and during the past year more than 400 serums were received for neutralization tests against the epidemic keratoconjunctivitis virus. These serums came from all parts of the country and in well over 90% of the cases the results of the neutralization tests were in agreement with clinical findings.

No reports of epidemic keratoconjunctivitis outbreaks in the United States are available during the last 10 or 12 months. Certainly there have been no extensive outbreaks and it is unlikely that the disease is a problem of importance from the public health point of view or a military point of view.

Work on the relationship between strains of epidemic keratoconjunctivitis and herpes virus has been carried on in Major Sanders' laboratory during his assignment on another project.

The laboratory for the study of epidemic keratoconjunctivitis is to be closed for the time being.

Liaison with the Virus Laboratory of the Army Medical School.- The Commission has attempted to keep in close touch with this laboratory and has been fortunate in having Col. Harry Plotz and members of his staff in attendance at all of our meetings. We have been grateful to him for keeping us informed about specimens sent to the Army virus laboratory, in which neurotropic viruses or their antibodies are suspected.

The Neutralizing Antibody Test.- Information has come from several sources that certain new facts are coming to light about virus neutralization tests.

These are of interest to this Commission in that a special committee was formed in 1941 to standardize these tests.* Capt. L. Whitman, of the Army Medical School, has indicated that some fairly labile substance perhaps similar to complement is lost in certain sera when the sera are diluted. The absence of this substance diminishes the neutralizing capacity of the serum. This supplementary substance is also destroyed by heat. Dr. Isabel Morgan has made somewhat similar observations with regard to sera which lose their neutralizing antibody capacity on storage. Dr. Hammon also believes that the technique of neutralization tests reserves a re-study at this time and this matter is now under consideration by the Commission.

Poliomyelitis.- This disease has never reached a high prevalence in American troops. In the summer of 1943, the United States experienced its third largest epidemic of poliomyelitis and during this period the rates in the troops stationed in the United States did not go to high levels. Nevertheless poliomyelitis has proven to be a greater problem than was anticipated two years ago. It was a sufficient cause for concern so that a special conference on poliomyelitis was held at the direction of the Surgeon General in September, 1943. This was done under the Division of Medical Sciences of the National Research Council acting for the Committee on Medical Research of the Office of Scientific Research and Development. The Commission has noted the valuable opinions expressed on poliomyelitis as a military disease at that time.

In the Middle East and Mediterranean area, poliomyelitis is a definite military problem. It has been common and severe in British troops. The rates in American troops in the U.S.A.F.I.M.E. have been about 10 times that seen in the United States. Strains of virus from the stools of those

*A standard Neutralization Test with the viruses of E.E. and W.E.E. and S.L.- Report by the Commission on Neurotropic Virus Diseases submitted to S.G.O., May, 1942.

cases have been isolated by the Virus Commission at the Middle East laboratory. From 15 cases of poliomyelitis, 9 such strains were isolated. From 18 cases of borderline or atypical poliomyelitis, no strains were isolated. This work has been of some interest to British medical officers in the Middle East because the technique of virus isolation from stools had not been used in their laboratories.

Supposedly, poliomyelitis in the civilian population of Egypt and Palestine is very uncommon, but investigations by our Commission on hospital statistics and also the records of private physicians revealed the fact that actually it is common in these areas and that a ten-year record of the cases indicates a rate which may not be different from those of the central or southern United States. The difference is that poliomyelitis does not appear in epidemic form in the Middle East. It is pointed out that the disease has been neglected there because of its failure to appear in epidemic form. Many cases are missed because they appear sporadically at times when physicians are not thinking of poliomyelitis. Certainly the epidemiology of poliomyelitis in tropical and sub-tropical countries deserves more consideration than it has received in the past.

Middle East Strains of Poliomyelitis Virus in the Cotton Rat.- From three strains of poliomyelitis received from the Middle East from Major van Rooyen, R.A.M.C., Dr. Olitsky, and colleagues have succeeded in establishing one strain in the cotton-rat and mice. From four strains collected in our own Middle East laboratory and studied in the United States by Dr. Ward, one has been established in the cotton-rat and mice. This is a high percentage of rodent adapted poliomyelitis strain. It has not yet been determined whether Middle East strains of poliomyelitis virus are particularly inclined to show this property of rodent adaptation more frequently than do domestic strains. Work on this subject is in progress.

Susceptibility of East African Monkeys to Poliomyelitis Virus Infection.- Different species of monkeys differ materially in their susceptibility to infection with the poliomyelitis virus. Five species were used at our Middle East laboratory, of which three had never been used before in poliomyelitis virus work. Of these the grivet and vervet monkeys of East Africa were found to be highly satisfactory for poliomyelitis work.

Epidemiological Surveys of Poliomyelitis in Civilian and Military Centers in the United States During 1943.- These were conducted by Dr. J. L. Melnick in Chicago and in New Haven, Connecticut. New tests in which the virus has been found in sewage have been reported by him. Similar epidemiological studies have been carried on by Dr. Hammon in Arizona and California. In one unusual epidemic which occurred among Navy cadets at Camp San Luis Obispo, the cases were suspected at one time of being due to Russian encephalitis. Stool specimens from these patients, however, yielded poliomyelitis virus.

It is pointed out that in spite of many new findings in the field of poliomyelitis, no new methods of control are recommended.

Respectfully submitted,

John R. Paul, M.D.
Director

SCIENTIFIC REPORTS TO THE S. G. O.

May 1, 1943 - April 1, 1944

Middle East "Virus Commission" Reports

The following Reports of work done in the Middle East have been issued by this Commission: All of them have been submitted to the Office of the Chief Surgeon, U.S.A.F.I.M.E., and to the Division of Preventative Medicine, Surgeon General's Office.

- May 1943 1. Preliminary Observations on the Effectiveness of Certain Repellents on Phlebotomus papatasi, by Major A. B. Sabin, M.C.
- July 1943 2. Sandfly (Pappataci) Fever as a Military Disease in the Middle East - prepared at the request of Colonel C. F. Sams, M.C. This article has formed the basis of Circular Letter No. 31, entitled: Sandfly (Pappataci) Fever, issued by the Office of the Chief Surgeon, Medical Section, U.S.A.F.I.M.E.
- Sept. 7, 1943 3. Estimate of the extent to which Sandfly Fever was and is a problem among American Forces in Sicily, by Major A. B. Sabin, M.C. Prepared for and submitted to the Chief Surgeon, Seventh Army.
- Sept. 24, 1943 4. Interim Report of the Activities and Studies carried out by the Virus Commission in the Middle East and in Sicily (April - October, 1943), by J. R. Paul, Major A. B. Sabin, M.C., and Major C. B. Philip, Sn. C.
- Nov. 16, 1943 5. Report on Infectious Hepatitis among American Troops in Sicily, by J. R. Paul and Capt. W. P. Havens, Jr., M.C. Prepared for and submitted to the Chief Surgeon, Seventh Army, and to the Chief Surgeon, N.A.T.O.U.S.A.
- Dec. 4, 1943 6. Preliminary Report on Infectious Hepatitis in American Troops in the Middle East and North Africa, by J. R. Paul.
- Feb. 1944 7. Poliomyelitis in British and American Troops in the Middle East, The Isolation of Virus from Human Faeces, by J. R. Paul, Capt. W. P. Havens, Jr., M.C., and Maj. C. E. van Rooyen, R.A.M.C. (To be published)
- Feb. 1944 8. Susceptibility of East African Monkeys to Experimental Poliomyelitis, by J. R. Paul. (To be published)